Titel der Arbeit:
The Neural Representation of Taste Perception

DISSERTATION
zur Erlangung des akademischen Grades

Doctor rerum naturalium
(Dr. rer. nat.)

eingereicht an der
Lebenswissenschaftlichen Fakultät der Humboldt-Universität zu Berlin

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Tag der mündlichen Prüfung: 21.03.2019

Abstract

The sense of taste serves a basic function in human survival by scrutinizing substances as to their edibility, and plays a more specific role for health by determining food selection in societies of overabundance. It is a key component of the perception of flavor – one of the most complex human behaviors – which, in light of the obesity epidemic, garners increasing scientific interest. Historically, the human gustatory system has been strikingly neglected in research endeavors of human perception, likely due to difficulties with precise stimulus control. Only recently – by virtue of technological advances – have researchers been enabled to devise experimental setups which live up to high scientific standards, such as reliable timing, quantity and location of stimulation.

In this dissertation, I investigated the cortical signature of taste information coding, specifically synchronized neural activity or *brain oscillations* which reflect one of the key mechanisms of neuronal communication (see Study 1: The time-frequency dynamics of gustatory processing). I found that the human brain recruits very-slow wave delta oscillations to process taste information, and that the emergent patterns were taste-specific and predictive of response behavior. This suggests that these oscillations represent both the mechanism of information transmission across the network, and at the same time the coherent code with which to extract details of a taste event, so that distant non-sensory areas gain access to information that will guide for instance decision-making.

Subsequently, I examined whether the processing sequence involved in taste recognition unfolds in distinct computational states (i.e. with separable detection and categorization steps), or whether a temporal priority is absent in light of the important proxy function a taste category exerts for a sensory gateway like the sense of taste (see Study 2: The processing sequence involved in taste recognition). The findings were mixed in that the processing sequence varied with taste contrast, such that hedonically distinct tastes were categorized as soon as they were tasted. This suggests that valence may be processed in parallel to sensory taste information, reducing processing times due to a sharpening of the taste category, or by replacing the need for categorization. This result closely aligns with the established processing cascade in olfactory perception, the other chemical sense whose ultimate goal is also the determination of edibility (or broadly speaking: approach versus avoidance behavior).

Finally, I compared the evoked gustatory response patterns between normal-weight and obese individuals in order to test them for quantitative and qualitative differences in their activation patterns, and their respective temporal characteristics (see Study 3: Contrasting taste processing between normal-weight and obese individuals). The results suggest based on indistinguishable activation patterns that both groups recruit the same mental processes in order to encode a taste event. However, the taste representations subside earlier in obese individuals, directly coinciding with the offset of stimulation. While the effect is brief and requires replication, this finding does align with the observation of hypoactive neural responses in obesity such as an attenuated experience of reward from food. In combination with increased sensitivity to food cues, this shorter-lived taste experience could constitute a further piece in the vicious cycle which eventually leads to obesity.

Altogether, the research laid out in the current thesis furthers our understanding of the human gustatory system, yet much more work is needed to be done before the most pressing issues of our times can be adequately addressed. Indeed, faced with the food-related health crisis of obesity in the Western world, there is an undeniable urgency to better understand one of the key systems involved in flavor perception.

Zusammenfassung

Der Geschmackssinn (engl. *taste*) dient grundlegend dem menschlichen Überleben, indem er Substanzen auf ihre Essbarkeit hin überprüft, und darüber hinaus erfüllt er eine spezifischere Rolle für die Gesundheit, indem er die Lebensmittelauswahl in Gesellschaften mit Nahrungsüberfluss bestimmt. Er ist eine Schlüsselkomponente der Geschmackswahrnehmung (engl. *flavor*) – eines der komplexesten menschlichen Verhalten – das angesichts der Adipositas-Epidemie ein zunehmendes wissenschaftliches Interesse anzieht. Historisch gesehen wurde das menschliche Geschmacksystem in der Wahrnehmungsforschung auffallend vernachlässigt, höchstwahrscheinlich aufgrund von Schwierigkeiten bei der präzisen Stimuluskontrolle. Erst in jüngster Zeit konnten Forscher aufgrund des technologischen Fortschritts experimentelle Abläufe entwickeln, die den hohen wissenschaftlichen Standards, wie beispielweise exakter Stimulationszeitpunkt, -menge und -lokation, entsprechen.

In der vorliegenden Dissertation habe ich die kortikale Signatur der Geschmacksenkodierung hinsichtlich synchronisierter neuronaler Aktivität oder *Hirnschwingungen* untersucht, die einen der Schlüsselmechanismen der neuronalen Kommunikation repräsentieren (siehe Study 1: The time-frequency dynamics of gustatory processing). Ich habe herausgefunden, dass das menschliche Gehirn sehr langsame Delta-Wellen rekrutiert, um Geschmacksinformationen zu verarbeiten, und dass die evozierten neuronalen Antwortmuster geschmackspezifisch und prädiktiv für das Antwortverhalten waren. Dies deutet darauf hin, dass diese Hirnschwingungen sowohl den Mechanismus der Informationsübertragung innerhalb des gustaotirschen Netzwerkes darstellen, als auch gleichzeitig den kohärenten Code, mit dem Details eines Geschmacksereignisses extrahiert werden können, so dass entfernte, nicht-sensorische Hirnareale Zugang zu Informationen erhalten, die beispielsweise die Entscheidungsfindung beeinflussen.

Anschließend habe ich untersucht, ob sich in der Verarbeitungssequenz zur Geschmackserkennung unterscheidbare computationale Zuständen beobachten lassen (d.h. mit trennbaren Detektions- und Kategorisierungsschritten), oder ob eine zeitliche Priorität aufgrund der wichtigen Proxyfunktion fehlt, die eine Geschmackskategorie für ein sensorisches Gateway wie den Geschmackssinn inne hat (siehe Study 2: The processing sequence involved in taste recognition). Die Ergebnisse waren insofern nicht eindeutig, da die Verarbeitungssequenz mit dem Geschmackskontrast variierte, so dass hedonisch unterschiedliche Geschmäcker gleichzeitig detektiert und kategorisiert wurden. Dies deutet darauf hin, dass die Valenz parallel zu sensorischen Geschmacksinformationen verarbeitet werden kann, was die Verarbeitungszeiten aufgrund einer Schärfung der Geschmackskategorie reduziert oder die Notwendigkeit einer Kategorisierung ersetzt. Dieses Ergebnis steht in engem Zusammenhang mit der etablierten Verarbeitungskaskade in der Geruchswahrnehmung, dem anderen chemischen Sinn, dessen oberstes Ziel auch die Bestimmung der Essbarkeit (oder allgemeiner: Annäherungs- versus Vermeidungsverhalten) ist.

Schließlich habe ich die evozierten geschmacklichen Antwortmuster zwischen Normalgewichtigen und fettleibigen Individuen verglichen, um sie auf quantitative und qualitative Unterschiede in ihren Aktivierungsmustern und entsprechenden zeitlichen Verläufen zu testen (siehe Study 3: Contrasting taste processing between normal-weight and obese individuals). Die Ergebnisse deuten darauf hin, dass – auf der Grundlage nicht unterscheidbarer Aktivierungsmuster – beide Gruppen die gleichen mentalen Prozesse rekrutieren, um ein Geschmackserlebnis zu verarbeiten. Die Geschmacksrepräsentationen lassen jedoch bei adipösen Individuen früher nach, und zwar direkt mit dem Ende der Stimulation. Obgleich dieser Effekt kurz ist und eine Replikation erfordert, stimmt dieser Befund mit der Beobachtung hypoaktiver neuronaler Reaktionen bei Fettleibigkeit überein, wie beispielweise einem abgeschwächten Belohnungserleben durch Essen. In Kombination mit einer erhöhten Sensibilität für Lebensmittelsignale könnte dieses kürzere Geschmackserlebnis ein weiteres Stück im Teufelskreis sein, das schließlich zu Fettleibigkeit führt.

Insgesamt vertiefen die in der vorliegenden Arbeit dargestellten Ergebnisse unser Verständnis des menschlichen Geschmackssystems, doch es bedarf noch weiterer Forschung, bis die drängendsten Fragen unserer Zeit angemessen beantwortet werden können. Angesichts der ernährungsbedingten

Gesundheitskrise in der westlichen Welt besteht eine enorme Wichtigkeit, eines der Schlüsselsysteme für die Geschmackswahrnehmung besser zu verstehen.

Contents

1 Introduction

In light of radically changing diets and their harmful health outcomes, the US government began to establish the first dietary guidelines in the 1970s to face this looming threat to public health (see Oppenheimer & Benrubi, 2014). Obesity and its associated chronic diseases were understood as a problem of overconsumption and undernourishment, presumably as a consequence of undereducation. The gist of the first guidelines published in 1980 (US Department of Health and Human Services) can be summarized as "eat less, avoid (saturated) fat and sugar, and eat more plants". Since then, the guidelines have been updated every five years, while staying true to its principal message. Yet, 40 years later, public health is in a state of crisis, with approximately 40% of the US population being obese, and a continuously rising trend among both adults and youths (Hales, Carroll, Fryar, & Ogden, 2017). Unsurprisingly, the rest of the world closely follows suit the US example, sharing in the challenge to face this now global pandemic (Ng et al., 2014).

Where did we go wrong? Despite well-meaning attempts to educate the public, nine out of ten Americans do not consume the minimum recommended amount of vegetables a day (which generously considers French fries, which – along with tomatoes in the form of pizza sauce – constitute the majority of vegetable intake[1]). Worse, only one in 500 children attain the minimum consumption of dark leafy green vegetables daily (cf. Krebs-Smith, Guenther, Subar, Kirkpatrick, & Dodd, 2010). Consequently, nearly the entire US population consumes a diet that is out of balance with the recommendations. A recent examination of the best diet for health arrives at broad principles that sound familiar, yet the authors conclude that the current situation is a testament to the failure of converting this knowledge into action (D. Katz & Meller, 2014). Thus, is the obesity crisis really a problem of undereducation? Typically, adherence to the diet regimen, or more broadly dietary recommendations, is measured as an aside – as a control for the outcomes of interest. This highlights a core aspect missing in the debate of healthy eating: what determines people's food choices? Is it entirely an issue of adequate information? Perhaps instead, food consumption should be understood as a multifactorial process to which hedonic and broader psychological aspects (such as food appearance, context, etc.) are likely to contribute just as much as health-related information.

Indeed, rather than thinking of foods solely in terms of their macro- and micronutrients, it will be helpful to better understand the "human brain flavor system" (Shepherd, 2011). Driven by sales figures and without a deeper understanding of or interest in the underlying mechanisms, the food industry capitalized on the observation that hyper-processing foods to be sweeter, saltier, and fattier incites cravings and overconsumption. Given that the direction of the industry is diametrically opposed to public health interests, a rigorous investigation is required to gain a more fine-grained understanding of how flavor perception arises (beyond crafting the perfectly pleasurable food), and ultimately, how healthier unprocessed food options may be able to compete hedonically with processed foods (ideally without changing the food itself). After all, people tend to eat what they like, and flavor is in the brain, not the food (Shepherd, 2011; see also Small 2012). In fact, because not everyone is becoming obese in an environment that presumably is conducive to obesity, differences between individuals in their neural encoding of foods garner increasing interest (Small, 2009).

1.1 The Neural Encoding of Foods

Essentially, the flavor experience associated with a food is the perceptual outcome of the neural integration of sensory inputs from multiple modalities – which, at its core, are the gustatory (taste), olfactory (smell) and somatosensory sensations that originate from the mouth at the same point in

[1] https://www.ers.usda.gov/data-products/chart-gallery/gallery/chart-detail/?chartId=58340

time (Small, 2012). Interestingly, other modalities that are not as intuitively linked with flavor may exert considerable influence on the eventual flavor percept, as for instance demonstrated by a seminal study in which wine tasters described a wine in accordance with its color (red) rather than its smell (white wine; Morrot, Brochet, & Dubourdieu, 2001). Moreover, the perceptual systems are connected with other systems for learning, memory and emotion, in order to establish food preferences and cravings, making flavor perception one of the most complex human behaviors (Shepherd, 2006). Given its complexity, scientific scrutiny of flavor perception necessitates the decomposition of the experience into its individual components or systems, respectively, with a special focus on the chemical senses of taste and smell as the principal gateways for assessing food palatability. Unfortunately, the attention given to these two sensory systems has been more than lacking in the past, and only recently has the interest (but also methods of stimulus delivery) started to catch up to the more classic sensory fields of vision and audition (cf. Lundström, Boesveldt, & Albrecht, 2010). As a consequence, our basic understanding of the neural processing of the chemical senses, particularly the sense of taste (cf. Ohla, Busch, & Lundström, 2012), is still lacking (cf. Small & Prescott, 2005).

1.2 Taste Perception

Due to the often synonymous treatment of ”taste” and ”flavor” (exemplified by the fact that the two are sharing the same word in German: *Geschmack*), the sense of taste naively receives the majority of the credit when it comes to flavor perception. In truth though, the primary role of the gustatory system is a highly functional one, as it subjects food (or rather any substance which enters the mouth) to chemoreceptive scrutiny (Lindemann, 2001). Therefore, the gustatory system can be thought of as the principal gateway to determine edibility, ultimately deciding intake or expulsion. It does so by categorization of *basic taste qualities* which broadly serve as a proxy to physiologically relevant features: **sweet** and **savory** (umami) tastes result from the presence of carbohydrates and amino acids, respectively, which signal energy content and likely favor palatability and ingestion; a **salty** taste signals electrolytes, which are essential to maintain the balance of bodily fluids, thus intake will be finely attuned to current demands; a **sour** taste may warn of spoilt food, and likewise a **bitter** taste may alert to the presence of toxic substances, likely leading to rejection of food (Lundström et al., 2010; Shepherd, 2011). Corroborating the gustatory sense’s critical function, even newborns reliably demonstrate basic taste discrimination by responding with specific facial expressions and lower-face actions to taste cues, as for instance sweet stimulates sucking and bitter leads to mouth gaping (Rosenstein & Oster, 1988), actions which itself are considered to indicate innate approach and avoidance behavior to tastes.

1.3 Taste Periphery and Transduction

Taste perception begins in the oral cavity, mainly on the tongue with stimulation of taste buds[2]. These buds are the peripheral sensory organs of gustation and contain clusters of columnar sensory cells that express receptors for the basic taste qualities (in appearance reminiscent of a garlic bulb; Roper & Chaudhari, 2017; see also Figure 1.1). Taste buds are distributed among papillae in the epithelium of the tongue which are described according to their shape and size: small mushroom-like (fungiform) papillae on the anterior and middle part of the tongue, medium folds (foliate) papillae on the sides at the back, and large round (circumvallate) papillae in the middle across the back (Shepherd, 2006). The cells within the buds come in three main types (type I, II, and III, numbered in accordance with their function and in order of their relative abundance), and their receptors are distinguished mainly into classes of G protein-coupled receptors (GPCRs) and ion channels. Importantly, salty and sour tastes activate ion channel receptors, whereas sweet, bitter and umami act on GPCRs (e.g. leading to different transduction speeds).

[2]Similar receptors were also discovered at the back of the mouth, i.e. in the epithelium of the palate, oropharynx, larynx and upper esophagus, but their functions are not yet fully understood (Lundström et al., 2010).

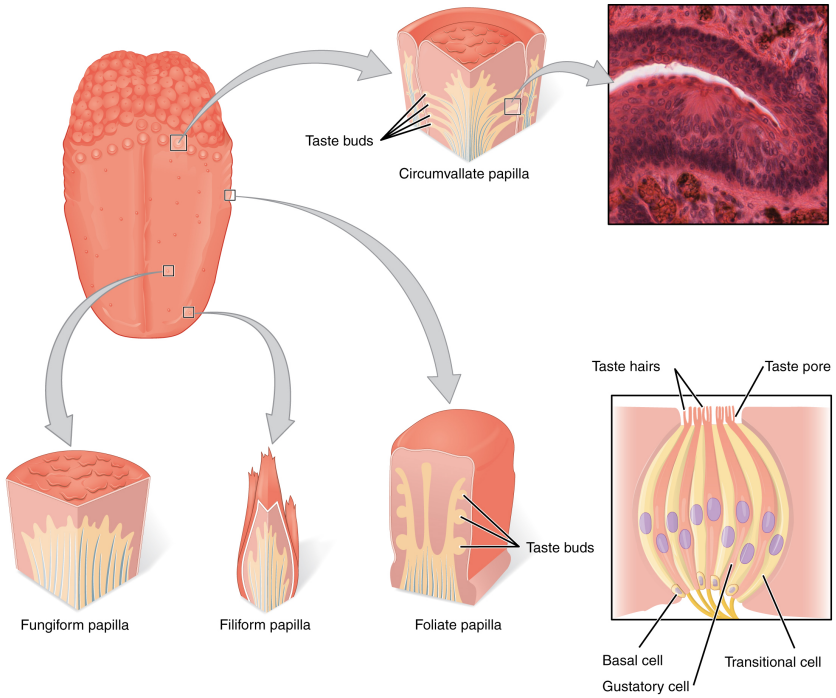

Figure 1.1: Taste periphery. Taste perception begins in the mouth by chemical stimulation of taste receptor cells (TRCs) which are bundled together in taste buds, small structures located within papillae across the surface of the tongue, palate, epiglottis and esophagus. Papillae are categorized in three different forms based on their shape and size: fungiform, foliate, and circumvallate papillae. The TRCs within the buds are innervated directly by afferent fibers of the chorda tympani of the facial nerve, the glossopharyngeal nerve, and the vagus nerve.

Image: The Tongue [CNX Anatomy and Physiology textbook 8.25]. (2016). Retrieved October 9, 2018 from: https://cnx.org/contents/FPtK1zmh@8.25:s3XqfSLV@7/Sensory-Perception

Taste receptor cells have no axons which carry their responses to the brain, but interact with the endings of the chorda tympani of the facial nerve (cranial nerve [CN] VII), the glossopharyngeal nerve (CN IX), and the vagus nerve (CN X). These taste nerves converge on neurons in the nucleus of the solitary tract in the brainstem, from where gustatory fibers project directly to the thalamus[3] (Carleton, Accolla, & Simon, 2010; Lundström et al., 2010). From here, the signal is further relayed to the primary gustatory cortex, which is typically localized in humans as the anterior parts of the insula and overlying frontal operculum.

The nature by which taste information is transmitted from the periphery to the central nervous system, and particularly how the different taste signals are encoded, remains an open debate with two major opposing views. The **labelled-line** theory assumes that individual taste bud cells exclusively identify one type of taste quality and connect with afferent fibers that are dedicated to that quality, so that the totality of the taste information is transmitted via segregated pathways ('labelled' lines) into the brain (Barretto et al., 2015), where each quality is represented by its own separate cortical field (Chen, Gabitto, Peng, Ryba, & Zuker, 2011). This coding scheme can be understood as a wire which directly connects the periphery with higher areas in the central nervous system, and variations in intensity are conveyed by modulated neuronal activity (cf. Carleton et al., 2010). The alternative, **across-fiber pattern** theory states that taste information is transmitted by the combinatorial activity of ensembles of diverse afferent fibers, such that the overall activation pattern signals taste quality and quantity (i.e. intensity) and is encoded by broadly tuned neurons (for an extensive discussion cf. Erickson, 2008). The latter point pertaining to broad tuning sensitivity confers the advantage that only few taste sensors and taste neurons, respectively, are required to encode many different tastes[4] (e.g.

[3] In contrast to the olfactory system whose nerves enter the brain closely to the highest cognitive centers, the gustatory system connects first with the autonomic nervous system. Thus, one may speculate that this allows for a multisensory flavor sensation to be analyzed at both the highest cognitive level and at the level of the most vital bodily functions (Shepherd, 2006).

[4] Note that for instance sweet or bitter are categories (or *qualities*), and that there are many different chemical compounds which can elicit these taste sensations. Simply think of the many different kinds of sweeteners in everyday use. Interestingly, sweet and bitter compounds have also been shown to be mediated by overlapping transduction mechanisms (Wong, Gannon, & Margolskee, 1996).

thousands of bitter compounds can be detected by the activation of only approximately 25 bitter taste receptors; Meyerhof et al., 2010), that is that gustatory coding can be thought of as highly dynamic and distributed (D. B. Katz, Nicolelis, & Simon, 2002; Simon, de Araujo, Gutierrez, & Nicolelis, 2006) and responsive to learning (Carleton et al., 2010). Indeed, this combinatorial coding scheme would also be in line with what has been established in other sensory systems, for instance for color vision and odor recognition (Malnic, Hirono, Sato, & Buck, 1999).

1.4 Neural Taste Processing

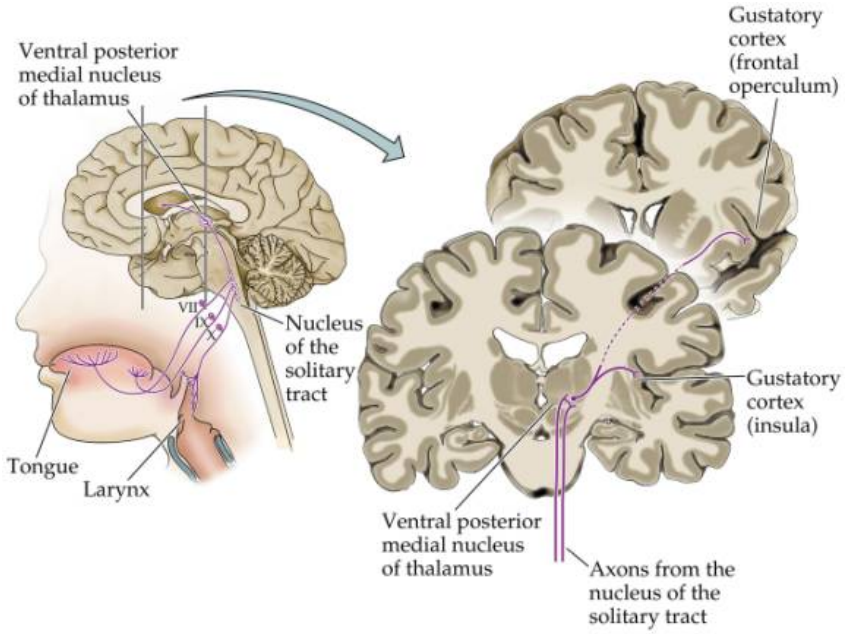

Figure 1.2: Taste pathway. Taste information is relayed by the three cranial nerves (VII, IX, and X) to the ventral posterior medial nucleus of the thalamus, from where information is further transmitted to the primary gustatory cortex which includes the insula and frontal operculum

Image: [Untitled illustration of the gustatory pathway]. Retrieved October 7, 2018 from: www.rci.rutgers.edu/~uzwiak/AnatPhys/Sensorysystems.html

To this day, most knowledge pertaining to the neural representation of taste stems from functional magnetic resonance imaging (fMRI) studies, which by design aggregate responses over periods of seconds to address where activation takes place. As a consequence, they are rather forgiving of imprecise stimulus delivery methods (essentially circumventing the major challenge faced by investigations of temporal dynamics), so that one common and practical solution oftentimes has participants initiate the stimulation themselves by sucking on a tube (which will then deliver a liquid taste solution). FMRI studies using such liquid oral taste stimuli have repeatedly shown neural activation in the insula, the orbitofrontal cortex (OFC), and the anterior cingulate cortex (Ohla et al., 2012), though the precise locations remain an open debate. A recent meta-analytic estimation of activation likelihood across 15 fMRI taste studies further refined the localization of the cortical taste-responsive areas by reporting a highly probable involvement of several areas situated within the insula and overlying frontal operculum, and OFC[5] (Veldhuizen et al., 2011; for a visualization of the taste pathway from periphery to primary gustatory areas, see Figure 1.2). The general consensus from past research broadly regards the insula as the primary taste area[6] which processes the sensory information of the taste response such as

[5]Significant activation probabilities were reported for the bilateral anterior insula and overlying frontal operculum, bilateral mid dorsal insula and overlying Rolandic operculum, and bilateral posterior insula / parietal operculum / postcentral gyrus, left lateral OFC, right medial OFC, pregenual anterioral cingulate cortex, and right mediodorsal thalamus (cf. Veldhuizen et al., 2011).

[6]Again, the precise location of this 'primary' area is debated in two opposing views – based on the methodology employed. FMRI findings localize this area to the transition between insula and frontal operculum, whereas MEG findings point to the transition between insula and parietal operculum (cf. Ohla et al., 2012).

intensity (Grabenhorst, Rolls, & Bilderbeck, 2007) and taste quality (Schoenfeld et al., 2004). The OFC is referred to as the secondary taste area which processes hedonic aspects of taste (Grabenhorst et al., 2007; Kringelbach, O'Doherty, Rolls, & Andrews, 2003).

The purpose of aforementioned hemodynamic measures is to investigate where cortical activation takes place in response to a taste event. Such information may prove useful to elucidate instances of pathophysiology pertaining to taste ability (e.g. in case of brain lesions), or altered neural hedonic and reward responses, which is of notable interest in understanding obesity. They cannot (nor do they intend to) address when information emerges during gustatory processing, which could be useful in establishing a hierarchy of importance among taste features for a more basic understanding of the taste system, or to determine whether an event (i.e. whichever condition the experimental stimulus represents) influences sensory activity (shortly after stimulus onset) or higher-level cognitive processes (hundreds of milliseconds later; for an insightful example of such an investigation see Luck & Hillyard, 1999). For instance, one may ask whether attentional manipulation (such as food packaging) influences early sensory taste processing or taste-related memory retrieval and decision processes. Alternatively, time-frequency dynamics (oscillations or "brain waves") may grant insight into complex network activity – a likely appropriate description of the gustatory system (cf. D. B. Katz et al., 2002) – the disturbance of which recently lead to the concept of oscillopathies in neurodegenerative diseases (cf. Nimmrich, Draguhn, & Axmacher, 2015). Indeed, furthering our understanding of such cerebral gustatory processing dynamics is the primary focus of the present work.

To this end, measurement techniques with high temporal resolution such as electroencephalography (EEG) or magnetoencephalography (MEG) are required to record brain activity in quasi real-time (the other crucial factor of temporally reliable stimulation will be discussed in the section Gustometry). The very first attempts to record gustatory event-related potentials (gERP) date back as far as the late 60s and early 70s of the previous century (Funakoshi & Kawamura, 1968, 1971; Plattig, 1969), yet it was only recently with a resurging interest in gustometry as a research (Singh, Iannilli, & Hummel, 2011) and potential clinical tool (Hummel, Genow, & Landis, 2010) that further advanced the methodology (cf. Ohla et al., 2012). Due to the long-lasting neglect of the gustatory system in EEG research, many of the features that characterize the electrical cortical brain response during gustation are insufficiently determined. For one, the prototypical gERP waveform remains an open question, and likewise its cortical generators are not well described. Consequently, it is not clear which electrode locations are optimal in order to record a gERP in its entirety (or to analyze it, for that matter), and the issue is exacerbated by high across-subject variability, given that the gustatory signal likely originates from sources that are deeply situated within the cortex (which relates to the problem of volume conduction as signal dispersion depends on an individual's cortical folding).

ERPs are commonly described as a series of positive and negative voltage deflections from baseline activity (commonly called peaks or components) and are labelled according to the order or time of their occurrence post-stimulus (e.g. P1 for the first positive peak, or P100 at 100 ms, or N1/N100 for a negative peak, respectively; cf. Luck, 2014). Given an experimental condition, and a peak's temporal occurrence and associated topography, the deflection is then linked to a perceptual or cognitive process. For several tastes a first notable positive deflection has been reported around 130-150 ms (NaCl: Mizoguchi, Kobayakawa, Saito, & Ogawa, 2002; glucose: Wada, 2005; electric taste: Ohla, Hudry, & Le Coutre, 2009), likely constituting a sensory response. Indeed, studies combining EEG with electric taste stimulation (a current delivered to the tip of the tongue which elicits a unique, somewhat metallic taste, cf. Ohla et al., 2009; Plattig, 1969), and MEG studies using salty and sour tastes (e.g. Kobayakawa et al., 1996; Mizoguchi et al., 2002), consistently estimated the insula to be the origin of these P1 components, which were also most clearly observable over frontal electrode sites. In contrast, there has been no consistent report of a N1 component in the literature, with the exception of electric taste for which a negative deflection can be observed around 200 ms (Ohla et al., 2009), and salty taste at 265 ms (Mizoguchi et al., 2002). Other studies have reported positive deflections at later points such as 500 ms post-stimulus (e.g. Hummel et al., 2010; Singh et al., 2011) and referred to these as the P1, yet such inconsistencies between studies may potentially arise due to undetermined delays in the stimulus delivery, or due to a dismissal of earlier smaller components that suffered from poor signal-to-noise ratio (cf. Ohla et al., 2012).

For taste intensity, it had been argued based on observations from other sensory systems that

increased tastant concentrations would result in an increase in neuronal firing rates of taste-responsive cells, thereby generating gERPs with larger amplitude at the scalp (cf. Ganchrow & Erickson, 1970). Such could be confirmed for salty concentrations (Kobayakawa, Saito, Gotow, & Ogawa, 2008), while for sour concentrations both latencies and amplitudes were affected (Hummel et al., 2010). The reason for these quality-dependent findings may lie in the likely joint influence of taste quality and intensity on neuronal activity, and as long as either of these parameters is held constant there is little hope of clearly defining the unique impact of taste intensity.

In light of the uncertainty pertaining to the gustatory ERP – that is, its particular waveform or whether at all such a prototypical taste response can be measured at the scalp-level – it was most encouraging that a recent study demonstrated dissociable cortical taste patterns for each of four basic taste qualities (salty, sour, sweet, bitter) by time-resolved analysis of the entirety of the scalp EEG recordings (i.e. a multivariate classification analysis; Crouzet, Busch, & Ohla, 2015). This approach (the details of which will be described later in the section EEG Decoding) enabled the inquiry into neural taste representations without making prior assumptions, and supplemented earlier studies by finding that cortical taste response patterns encode taste quality as early as 175 ms post-stimulus. In the current dissertation, I have built upon this finding by refining the methodology further and by using the selfsame to probe multiple unresolved issues of gustatory research outlined below.

1.5 Research Questions

As briefly mentioned in the section Neural Taste Processing, one of the most notable unknowns with respect to the gustatory network is our lack of a mechanistic understanding of its functioning. While aforementioned fMRI studies have helped to resolve with increasing detail which areas of the brain constitute said network, information processing within the brain is best characterized by its time-frequency dynamics. One apparent and readily available feature of these dynamics is the rhythmicity of neuronal population firing rates (observable at the scalp as *oscillatory* activity which can be described by its frequency, amplitude and phase) which represents a key mechanism of neuronal communication across distributed areas (cf. Buzsáki, 2006). Studying these oscillations has very practical implications, as identifying the prototypical electrophysiological signature of taste perception not only helps researchers to locate the gustatory signal within the noisy electrophysiological recordings, but may find clinical applications in the restoration of normal taste function in neurodegenerative diseases or in reconstructing taste perception via brain-computer interfaces. Consequently, in Study 1: The time-frequency dynamics of gustatory processing I set out to investigate the frequency by which basic taste category information (e.g. salty, sweet, etc.) is neurally encoded.

Following up on the findings reported in Study 1: The time-frequency dynamics of gustatory processing, I examined the sequence with which taste information is encoded in the neural gustatory response. Such an investigation helps elucidate the temporal priorities enforced by a biological system, an inquiry of special interest for a sensory gateway like the gustatory one which potentially determines an organism's survival. For the other chemosensory system – the better studied olfactory sense – we know that detecting the presence of a smell precedes its identification (Olofsson, Bowman, & Gottfried, 2013), whereas in the visual system there has been evidence suggesting that one may know what category something belongs to as soon as one sees it (Grill-Spector & Kanwisher, 2005). To investigate the priority with which taste information is processed, I compared in Study 2: The processing sequence involved in taste recognition the neural and behavioral latencies of taste-detection and taste-discrimination in order to examine if one may know what taste category something belongs to as soon as one tastes it.

Finally, and again building upon the findings of Study 1: The time-frequency dynamics of gustatory processing, I wanted to compare the isolated gustatory signal between obese and normal-weight individuals. As mentioned in the Introduction, there is increasing interest in potential individual differences in how foods are neurally encoded (Small, 2009), of which the representation of taste is a chief concern. Evidence suggests that differences exist in the attention given to food cues (Hendrikse et al., 2015), and the processing of pleasure or reward in association with food (Stice, Spoor, Bohon, Veldhuizen, & Small, 2008), and perhaps also that taste sensitivity may differ between obese and normal-weight individuals (Hardikar, Höchenberger, Villringer, & Ohla, 2017; although there have been

conflicting findings). To adequately tackle the obesity epidemic, it is of great import to understand how far reaching the neural differences are when it comes to the perception of food, and more specifically the perception of taste. Thus, I examined in Study 3: Contrasting taste processing between normal-weight and obese individuals the potential differences in taste representations between obese and normal-weight individuals while tasting salty and sweet (the two taste categories that are most likely to lead to overconsumption).

2 General Methods

In this section I will describe general methods of measurement and analysis that I have made use of throughout the publications of the present dissertation. For the temporally sensitive measurement and reliable stimulation of ongoing neural gustatory activity I have used electroencephalography (EEG; briefly introduced subsequently in section Electroencephalography) in combination with gustometry, which I will outline in the necessary detail and historical context in order to appreciate the experimental setup throughout the investigations (see section Gustometry). For the analysis of the resulting recordings, I followed an information-based decoding approach, which is most commonly some incarnation of a multivariate pattern (classification) analysis, for which I will lay out in detail the motivation (see section Analysis).

2.1 Electroencephalography

Electrical brain activity originates as postsynaptic potentials of firing (i.e. responding) neurons. Ideally, one would measure a large enough number of such neurons (e.g. in a brain region of interest) and construct from the synchrony of their stimulus-induced activity a global pattern which represents the neural process of interest. Unfortunately, with the current state of technology, such a direct measurement of ongoing neural activity can only be achieved through invasive methods (i.e. opening the human skull and inserting electrodes into the brain). Instead, the neuroscientific field has advanced non-invasive methods that approximate neural activity in various ways.

EEG is one such method to capture global electrical activity – which is thought to represent the summed neuronal activity that originated from individual extracellular currents – by placement of electrodes on the scalp. The desired temporal resolution is achieved by a corresponding sampling rate that is implemented via modern amplifiers, thereby enabling quasi real-time recordings of electrical brain activity. Besides the ability to capture fast fluctuations of post-synaptic potentials, EEG is equally sensitive to tangentially or radially oriented electrical dipoles (i.e. neural signals in the sulci and on top of the gyri), so that the recorded activity is likely to originate from a larger area of the brain than other superficial measurement techniques such as MEG which purely relies on magnetic fields (note that the magnetic fields produced by radially oriented dipoles do not extend beyond a spherically symmetric volume conductor irrespective of the sensor orientation, cf. Baillet, Mosher, & Leahy, 2001).

The apparent downside to EEG is its poor spatial resolution due to a coarse spatial coverage with a comparably low number of sensors (64 in most instances) and a susceptibility to distortions from high-resistant tissues such as the skull and scalp tissue (cf. Nunez & Srinivasan, 2006). As a consequence of this volume conduction, the electrical field is dispersed across the scalp which induces variance that is difficult to factor out when estimating a signal's source (the so-called inverse problem). In fact, the measurements of a single electrode may reflect an average of tissue mass that contains synaptic activity of up to 1 billion neurons.

Despite this lack of detailed local information, scalp EEG provides a robust – albeit very large-scale – measure of cortical dynamic functioning. The finely time-resolved sequence of electrical activity reflects the flow of information through the brain, with each measurement point representing the current state of information-processing (Luck, 2014). Thus, it is an ideal tool to probe the neural processing dynamics across distributed brain areas, and consequently vital to understanding network functioning.

2.2 Gustometry

In order to obtain reliable information of cerebral gustatory timing one requires not only a method with high temporal resolution such as EEG, but one also has to meet particular demands of stimulus delivery (i.e. self-initiated sucking falls short of this ambition). Whereas a standard commercial screen operates at 60 Hz (which amounts to a refresh rate of approximately every 16 ms) to which the presentation of

visual stimuli can be aligned via cheaply available yet highly sophisticated graphics cards, the temporally and spatially exact stimulation of a tastant[1] is disproportionately more challenging (and obviously lacks any commercial interest). In fact, while the goal for reliable gustatory EEG recordings must be to maximize the precision of stimulus delivery by reducing externally induced trial-to-trial variability, the onset of gustatory stimulation may never be perfectly precise. For one, the mechanical delay between trigger and stimulation is influenced by various variables such as the viscosity of the solution, the flow rate of the system, the length of the tubing, etc., but also the stimulated peripheral area (tongue, oral cavity) may not be perfectly identical between trials (cf. Ohla et al., 2012). Whichever setup one arrives at, it needs to hold all of these parameters as constant as possible.

Besides the technical issues pertaining to the limitation of variation in the stimulus delivery, another concern is to have a taste stimulus with as much of a square shape characteristic as possible (i.e. a steep rise and fall time; Ohla et al., 2012). To elicit a strong and reliable percept, high tastant concentrations are required, yet the very same sensation needs to be cleared away just as reliably for a taste-free sensation between trials. Consequently, the experimental procedure demands an extensive rinsing protocol and lengthy inter-stimulus intervals (typically at least 20 seconds) to avoid sensory and neural habituation (which inevitably amounts to drawn-out taxing experimental sessions with a much lower amount of trials than in other non-chemosensory domains). Finally, a crucial challenge is to isolate the response of the gustatory system, for which unimodal stimulation is essential. This problem is rather non-trivial, as stimulation of a liquid is naturally multimodal, that is oral somatosensation and temperature are close companions of gustation, even in the absence of any oro-facial muscle movements.

In recent decades, various taste stimulation methods have been explored in order to address the aforementioned issues. The first rather curious apparatus consisted of a hinged spoon which delivered the taste solution (in a comparably large quantity) when tilted (Funakoshi & Kawamura, 1968, 1971). At the same time the potential of electrical taste stimulation was explored which applies electric pulses to lingual taste buds to elicit a unique taste percept with good stimulus control (Plattig, 1969), yet its ecological validity remains debatable. Other setups which followed consisted in a modified constant-flow olfactometer (using gaseous taste stimuli), and liquid stimulation devices without constant flow such as open-flow devices and sponge applicators (cf. Ohla et al., 2012). However, nowadays the established type of gustatory delivery is a setup in which the taste stimuli are embedded in a constant stream of a tasteless solution such as ionized water (pioneered by Kobayakawa et al., 1996). This constant flow habituates the lingual somatosensory system to eliminate a tactile response and holds the temperature of the liquid at body temperature, thus satisfying the demands of a unimodal gustatory stimulation.

The very same principle is put into practice in the GU002 gustometer (Burghart Messtechnik GmbH, Wedel, Germany) of which I have made use throughout the present work, which mimics the continuous flow of liquid through a 3.3 Hz frequency sequence of pressure-driven spray pulses (see Figure 2.1). The taste solutions are stored in separate bottles, from which individual lines extend, bundled together in a hose surrounded by water at body temperature, eventually leading to the stimulation setup – a spray nozzle which is positioned directly above the participant's protruded tip of the tongue. In this particular setup the participants do not swallow any liquids, instead those fluids accumulate in a bowl directly underneath the chin (for a more detailed description of the entire experimental procedure and visualization see Study 1: The time-frequency dynamics of gustatory processing). In our established stimulation protocol, the participants will receive three spray pulses of a tastant (extending over 900 ms), before the water stream resumes to quickly wash off any lingering taste. The reasoning behind the extended stimulation time is simply a safeguard in face of the unresolved issue whether gERPs have a clear offset response (as observed in the visual and auditory domain, but not in the olfactory system). If such were the case, overlapping evoked ON/OFF responses could pose a hindrance to subsequent analyses (cf. Ohla et al., 2012).

[1] The term *tastant* refers to the chemical taste stimulus which is typically a water-based liquid solution containing molecules associated with one taste category, e.g. NaCl for salty.

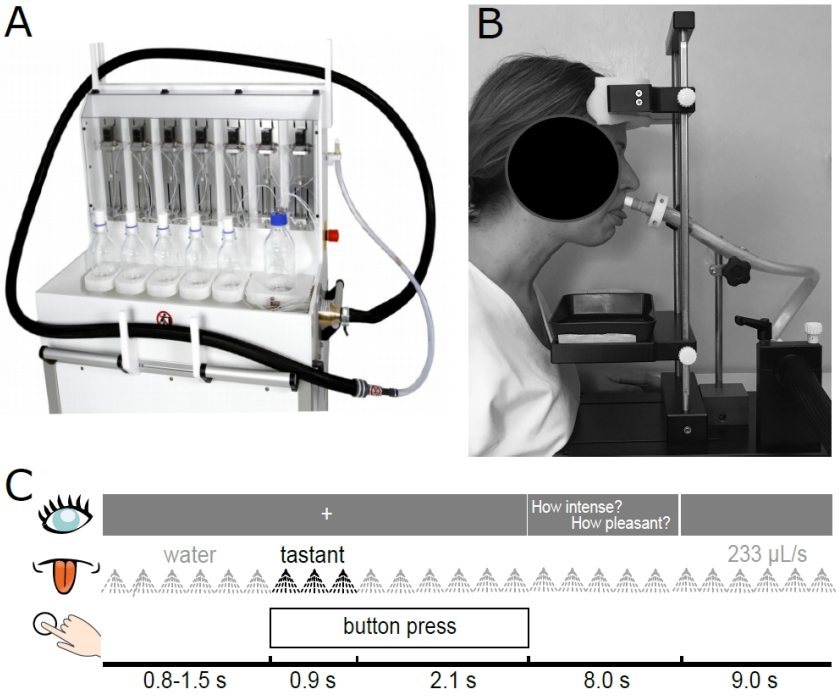

Figure 2.1: Experimental Setup and Paradigm. A: GU002 gustometer (Burghart Messtechnik GmbH, Wedel, Germany) used for continuous flow of liquid taste stimulation through a 3.3 Hz frequency sequence of pressure-driven spray pulses. Taste solutions are stored in separate bottles and transported via individual lines inside the EEG chamber. B: Participants lean forward into a head-rest and extend their tongue below a spray nozzle. The spray pulses are delivered directly onto the tip of the tongue, from where the liquid drips below into a bowl. C: A typical experimental protocol in which the participant continuously receives water, until the stimulation is cued with a fixation cross, followed by a variable inter-stimulus time, before the tastant is applied for the duration of 900 ms, after which the stimulus is rinsed off immediately with a stream of water. *Image adapted from Wallroth et al. (2018)*

2.3 Analysis

The underlying assumption to any measurement is that the signal of interest (i.e. the neurophysiological response to a stimulus) is systematic and non-random, as opposed to the background noise (either related to measurement error or cognitive interference) which is unsystematic and random. Therefore, the core challenge for neuroscientists is the extraction of this reoccurring pattern in response to an experimental condition. The conventional strategy of ERP analysis realizes this by aggregating the electrical activity across all repetitions to obtain an averaged waveform, a process which retains the time- and phase-locked signal and cancels out the non-systematic noise. However, this procedure is not without limitations, some of which I will discuss subsequently, before I will lay out the preferred information-based approach taken in the present work.

2.3.1 Limitations of ERP analysis

A typical EEG data set constitutes a three-dimensional matrix of trials (epochs in EEG nomenclature) of time series data at multiple electrodes; for instance 100 stimulus repetitions with a one second time series of 500 time points (i.e. a sampling rate of 500 Hz) at 64 electrodes results in 3.2 million data points for a single experimental condition and participant. Faced with such massive amounts of data and in need of statistical summary, the ERP approach offers an appealing simplification to the information extraction problem. First, based on prior knowledge, the researcher selects a subset of electrodes of the original measurement space which presumably are situated above the relevant brain area of interest, for instance occipital electrodes in order to study the visual system. Next, these local signals are aggregated to an average value, removing all spatial structure of the data. Finally, the electrical activity across all trials is averaged to a single value per time point, assuming that this mean value sufficiently, if not adequately, represents the signal of interest by retaining systematic deflections and cancelling out non-systematic deflections (i.e. erratic patterns attributed to noise will have positive and negative deflections across different trials which will average to a net value of zero). Given the above example, the sheer complexity of 3.2 million data points has been reduced to 500 averages, shrinking the massive multivariate problem to a much simplified univariate analysis which compares conditions based on a single activity value per time point.

In light of a lack of computational resources, this reductionist approach was historically well motivated. However, nowadays it no longer represents the state of the art, as it inevitably leads

to a loss of information and sensitivity (e.g. disregarding the topographical configuration), thereby potentially obscuring the effects of greatest neuroscientific interest. Moreover, the assumption that trial-to-trial variability equals noise may be unjustified, as for instance in the gustatory system such variability has been shown to reflect network state transitions evolving at different speeds so that the information conveyed by the state sequence would be lost by averaging (see Jones, Fontanini, Sadacca, Miller, & Katz, 2007). Finally, such an over-reliance on an average may skew conclusions because this metric is highly vulnerable to outlier values, and artifacts in EEG recordings often reach much higher amplitudes than the neural processes under study. Curiously, to address this particular problem, various elaborate preprocessing techniques (e.g. filtering, independent component analysis, automatic artifact rejection, etc.) have been continuously refined, leading this final overly simplistic analysis somewhat ad absurdum. Importantly, such processing treatments may themselves have adverse effects, which Luck (2014) summarized as "distortion of onset and offset times, unexplained peaks, artificial oscillations", and more humorously as "wildly incorrect conclusions, public humiliation by reviewers, and grant failure".

2.3.2 From activation-based to information-based analysis

Brain mapping and electrophysiological analysis alike have long since focused on discovering and describing activation patterns, and comparing these among experimental conditions (so-called 1st order statistic). Major caveats of this approach lie in the interpretation challenge posed by fine-grained patterns in the data, and the lack of correspondence of these activation patterns between participants, as they may be unique to each individual like fingerprints. To address this, conventional (univariate) analyses necessitate preprocessing techniques in order to smooth the data (e.g. anatomical warping, spatial smoothing, temporal filtering, and also averaging), and by isolating single locations from the overall pattern, so that the details in the activation patterns are removed and the challenges posed by high-resolution recordings are fundamentally evaded. While this certainly eases interpretation, the vast potential of high-resolution neuroimaging recordings remains largely untapped by virtue of discarded information and greatly reduced sensitivity (cf. Haynes & Rees, 2006; Kriegeskorte & Bandettini, 2007). Essentially, the data is fit to the analysis.

Principally, this activation-based approach is suited to detect generalizable changes in activation specific to the region(s) of interest by considering (somewhat arbitrarily, although not devoid of logic) the smoothed component in the data as the *signal*, and the fine-grained, inter-individually unique component *noise*. Under this paradigm, it is not the measurement, but rather the analysis which limits the sensitivity – and the hypotheses – of the study (Kriegeskorte & Bandettini, 2007). Specifically, the observation of smoothed activity may be insufficient in order to address the contents of a mental representation, that is one often cannot distinguish between the processing of information pertaining to the question of interest or broader, unspecific signal changes in response to the stimulus (e.g. can changes in prefrontal activity differentiate between working memory contents, or do they reflect unspecific updating signals; cf. Haynes, 2015).

Recently, a more general approach was popularized in the neuroscientific field which abstracts from the actual activation patterns by considering where or when the recorded brain activity contains information about an experimental condition (cf. Haynes & Rees, 2006; Kriegeskorte, Goebel, & Bandettini, 2006). Rather than aggregating the single-trial responses to a stimulus in order to obtain an average response, this approach models the stimulus-response relationship to test for the presence of information in individual activation patterns. Under this modelling paradigm, the analysis essentially fits the data, rather than the other way around – in fact, oftentimes raw or minimally processed data is acceptable. This abstraction towards information availability and contrasting (so-called 2nd order statistic) signified a crucial advance for the field of cognitive neuroscience. It affords a considerable increase in sensitivity and hypothesis complexity due to the ability to probe individual mental contents, and crucially, enables researchers to study neural dynamics, for instance changes in conscious perception (Haynes & Rees, 2006), or online multi-dimensional movement control (through so called brain-computer interfacing, see e.g. Wolpaw & McFarland, 2004).

In the neuroscientific nomenclature, the model which expresses the functional dependency between

stimulus and measurement is often referred to as a *decoder*, because it is a means to decode or read information which is *encoded* in the activation pattern. Decoding analysis is often also referred to as multivariate pattern analysis to contrast the conventional univariate approach, emphasizing the combination of local signals rather than their isolation (or aggregation). The most common variant of decoding is the response-pattern classification which refers to the modelling of the activity pattern to predict a stimulus or experimental condition (i.e. a categorical variable or *class*; cf. Kriegeskorte, 2011). Notably, the direction of the functional dependency between stimulus and response is reversed and modelled *backwards*, such that the function takes the activation pattern as an input and outputs (*predicts*) the stimulus class (cf. Haufe et al., 2014). However, the direction along which a model operates is in many cases not relevant to the interpretation, as it simply serves as a tool to demonstrate a statistical dependency between stimulus and response pattern (i.e. predictive information). For instance, if face stimuli selectively engage an area in the fusiform gyrus, then the activation of this area can also predict that the visual stimulus was a face.

Generally, this procedure unfolds in three stages of training (information extraction), testing (information generalization), and statistical comparison. First, during a training phase the model learns a (typically linear) decision boundary (i.e. a weight is assigned to each voxel or electrode) that best separates the measurement space for a binary problem[2]. Mathematically, this *learning* of a best fit between model and data refers to the convergence on a combination of projection weights that solve an optimization criterion. Typically, this constitutes two components of which the *loss* expresses the error generated by the current solution (i.e. how much does the prediction deviate from the truth), and the *regularization* expresses how likely the solution is according to prior knowledge (to prevent *over*fitting, e.g. counteract the overemphasis of certain electrodes). The way in which the decision problem is formulated determines what specific information will be extracted from the activation patterns, whereas anything else is treated as irrelevant[3].

Second, after the model has learned to maximally discriminate between the response patterns of two conditions (i.e. it has extracted *some* information), it is tested in how far it was able to extract *meaningful* information[4]. To this end, the model function receives previously unseen activation patterns as input (i.e. trials that were not part of learning) and outputs predictions as to the corresponding stimuli or experimental conditions (via projection of the measurements onto the learned weights). This process of separating the learning and testing phase so that the extracted information is generalized to new (unfitted) data is called *cross-validation* and is a useful way to obtain unbiased model performance estimates without actually having to collect new data (which is often quite costly in neuroscientific studies). Notably, the model is blind to the true conditions associated with the input activation patterns and will simply output its learned binary decision. Thus, the extracted information can also be extended to entirely new experimental conditions to explicitly test pattern similarity or learning (e.g. a model trained to differentiate between familiar fruity and floral odors can be applied to discriminate novel odors; Qu, Kahnt, Cole, & Gottfried, 2016).

Finally, if there was relevant information pertaining to the question of interest represented within the activation patterns, the model should do better than random guessing (i.e. 50% chance with a binomial confidence interval) during prediction. For statistical verification, the predictions are summarized to some performance metric (e.g. accuracy, area under the curve, entropy, etc.) and typically compared

[2]Although the problem is binarized, this does not necessarily mean that the decision reflects only two experimental conditions. For instance, one may contrast one condition against multiple other conditions to probe if there is unique information encoded in the activation pattern of that very condition.

[3]This is in contrast to the conventional ANOVA which includes all experimental conditions as factors and only then resolves significant effects by performing pairwise factor level testing.

[4]The learning algorithm will leverage *any* information at its disposal in order to minimize its prediction error. To accomplish this, it may adapt to unsystematic noise in the training data (to various degrees depending on the sophistication of the algorithm and the strength of the regularization). This generalization step is necessary to determine the quality of the learned information, i.e. if the model fit noise or true signal (assuming that there is no noise which is systematic to one of the conditions).

among experimental conditions or groups with a common statistical test (e.g. *t*-test, binomial test, etc.; but for caveats concerning statistical testing of information measures see Allefeld, Görgen, & Haynes, 2016). Hence, the eventual comparison pertains to the encoded information in the activation patterns, not the activation patterns themselves. This abstraction makes it possible to retain individual nuances in the activation patterns and leave it to the model algorithm to determine whether they are to be treated as signal or noise.

2.3.3 EEG Decoding

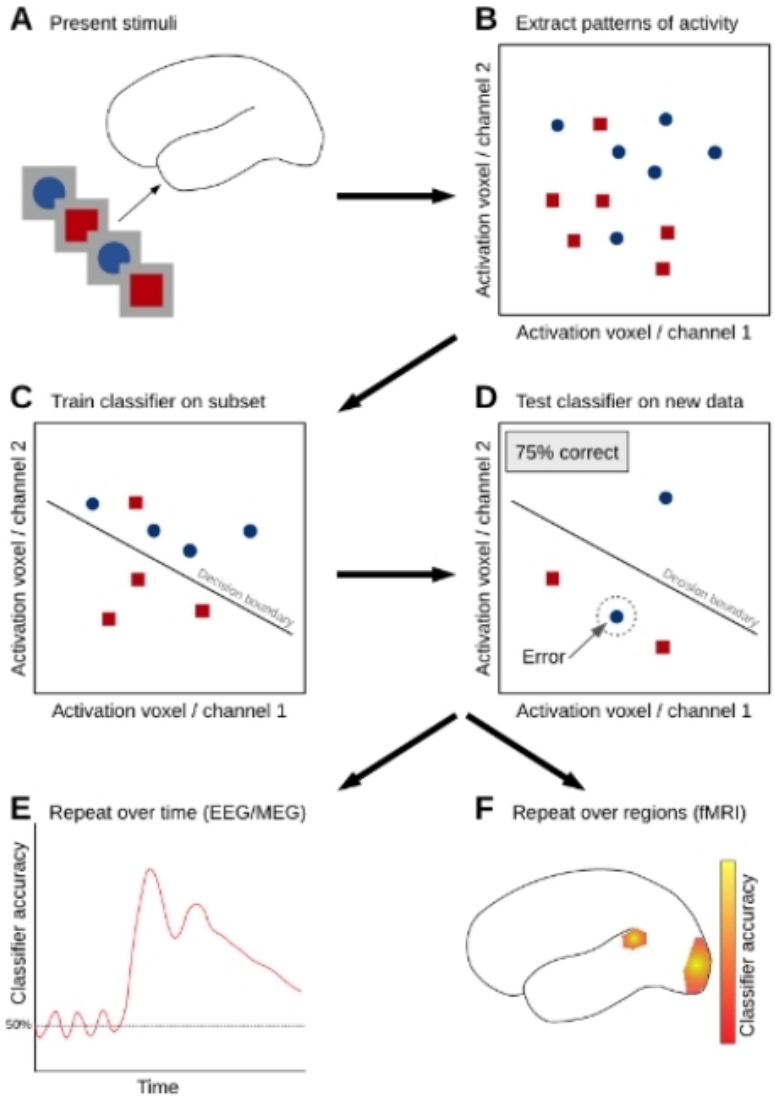

Figure 2.2: Decoding approach. The neural patterns (B) in response to a stimulus (A) are used to train a classifier (C), whose performance is evaluated on unseen data (D), a process that unfolds in a sliding time window for EEG data (E) or in a searchlight over the voxel space in fMRI (F); *image from Grootswagers et al. (2017)*

While similar in principle, the decoding of time-series neuroimaging data (e.g. EEG, MEG) slightly differs from the well-established decoding of fMRI data (for a review cf. Grootswagers et al., 2017; see also Figure 2.2). Rather than determining *where* in the brain information is represented (typically the goal of a searchlight fMRI classifier), time-series decoding tackles the issue of *when*. To this end, the decoder is commonly applied to the time-series in a sliding time-window in order to test for the presence of information time-point by time-point using the entire measurement space (i.e. amplitudes at all electrodes). Through this, the analysis can address for instance at which point in time the topographical configuration of the amplitudes is starting to differ, or is maximally discriminative, between experimental conditions.

Beyond providing information pertaining to timing parameters, an elegant extension of the sliding time-window approach (learning and testing at the same point in time) is the temporal generalization method (cf. King & Dehaene, 2014) which is extremely useful in facilitating our understanding of how

mental representations unfold over time. Using this, a classifier is trained at one time-point but applied to all time-points (or in one condition and applied to another), and its generalization (or lack thereof) provides an opportunity to examine the organization of cortical information-processing stages. For instance, if a classifier at 500 ms also discriminates better than chance at an earlier time point (e.g. 200 ms beforehand), one can infer that the same mental process is active at both times. Accordingly, this would suggest either an ongoing or recurring process (because the learned information at these time-points is applicable at either time), which can be resolved by inspecting the generalizability in-between the time-points (i.e. if there is no interruption the process is continuous). Conversely, if a classifier does not generalize, one can conclude that the mental processes between time-points differ (e.g. a chain of consecutive processes, rather than one ongoing lengthy process). Moreover, a classifier can be trained on one experimental condition and be generalized to another condition, both forward and backward in time, thus providing a means to explicitly test pattern similarity under consideration of potential latency shifts (e.g. a classifier trained to discriminate between salty and sweet tastes may also discriminate between sour and sweet tastes, but with a 50 ms time shift). In conclusion, the generalization of information (whether across time, conditions, groups, etc.) grants access to the vast potential of time-series neuroimaging data in elucidating neural dynamics, and thus enables the probing of highly complex hypotheses.

One specific example of this approach – and the starting point of the gustatory research laid out in the present work – is a study which successfully decoded taste quality information using scalp EEG recordings during a (delayed) four-taste categorization task (Crouzet et al., 2015). Multiple logistic regression classifiers were applied along the time-axis of the EEG data to address questions such as "Which taste is this?" (multi-class decoding, i.e. any of sweet, salty, sour, or bitter), or "Is this salty or one of the other three tastes?" (one-vs-the-rest decoding), or "Is this salty or sweet?" (one-vs-one decoding). These variations provide a detailed picture of when and how much taste quality information is represented cortically[5]. Moreover, the taste information was generalized across time in a four-by-four taste matrix (e.g. salty patterns are used to discriminate sweet, and vice versa) in order to formally test neural pattern confusion and latency shifts between tastes. If anything, this study demonstrated the usefulness of an information-based decoding approach to overcome the limitations imposed by conventional ERP analysis, and to promise a more nuanced access to the dynamics of human gustatory processing.

[5]For instance at which point in time does taste quality information emerge (or become maximal) at the scalp-level, how similar are the patterns between tastes (e.g. are there specific binary confusions), or whether decoding performance relates to behavioral outcomes (e.g. does a lower classification accuracy coincide with lower accuracy in the taste categorization task).

3 Study 1: The time-frequency dynamics of gustatory processing

This chapter refers to the publication in NeuroImage (Wallroth et al., 2018).

4 Study 2: The processing sequence involved in taste recognition

This chapter refers to the (open-access) publication in eNeuro (Wallroth & Ohla, 2018).

5 Study 3: Contrasting taste processing between normal-weight and obese individuals

This chapter refers to the (open-access) publication in Scientific Reports (Hardikar, Wallroth, Villringer, & Ohla, 2018).

6 General Discussion

The perception of flavor is one of the most complex accomplishments of the human brain, a feat which links multiple sensory and higher-order cognitive systems in order to elicit an unmistakable and multi-faceted experience (cf. Shepherd, 2006). Due to this complexity, the emergence of the holistic flavor percept is yet insufficiently understood, and investigations to remedy this fact necessitate the decomposition of the sum into its parts. One of the most crucial – yet poorly researched – constituents of the flavor experience is the sense of taste, precisely the focus of this dissertation.

Here, I investigated one of the key mechanisms by which the distributed gustatory network encodes taste information – the oscillatory activity in response to a taste stimulus (see Study 1: The time-frequency dynamics of gustatory processing). Studying these dynamics laid the groundwork for the remainder of this work, as it helped to isolate the distinct electrophysiological signature of gustatory processing from the summated neural responses that are encapsulated in the EEG recordings. Consequently, I examined the sequence of processing steps involved in taste recognition by comparing the de-noised gustatory response between variations of taste-related tasks designed to access a different candidate component of taste processing. This is useful in order to establish how quickly and to what extent the gustatory system encodes taste information in its processing sequence, whether a temporal priority can be discerned from the level of detail in the information encoded in the earliest taste response patterns, and whether the processing speed aligns flexibly with its context (see Study 2: The processing sequence involved in taste recognition). Lastly, I compared the neural taste representations between obese and normal-weight participants in a time-resolved contrast in order to examine potential differences in the way a taste sensation (and as a consequence the eventual flavor) is neurally encoded – such as differing signal strength, duration of encoding, or qualitative differences in the taste representations (see Study 3: Contrasting taste processing between normal-weight and obese individuals).

6.1 Slow-wave activity as a cortical signature of taste processing

In order to appreciate the findings of Study 1: The time-frequency dynamics of gustatory processing that delta oscillations encode taste information, a brief introduction of the key concepts is necessary. According to Fries (2015), the spatial activation pattern of a neuronal population in response to some input from the external world is commonly referred to as a *neuronal representation* of said input (i.e. the spatial configuration of activity somehow maps that stimulus onto the brain). The transfer of that representation across the trajectory of the brain's networks is considered *neuronal communication* (i.e. one ensemble of neurons sends information to a receiving ensemble). The transformation of that representation in the receiving neuronal population – to make sense of or translate the mapped input – is referred to as *neuronal computation*. Therefore, neuronal communication assumes a central role during information processing by implementing the creation of new representations – or essentially *meaning* – and its significance for human cognition has been extensively documented (for an overview, see for instance Buzsáki, 2006; Buzsáki & Draguhn, 2004; Fries, 2005, 2015). Classically, neuronal communication has been thought to be determined by structural connectivity in the brain and potential activity-dependent changes of said anatomical structure, yet due to several observations that activated neuronal ensembles tend to engage in rhythmic shifting of excitability it has been proposed that a key mechanism by which communication unfolds is synchronization (leading to the concept of "Communication through Coherence", cf. Fries, 2005, 2015). In fact, even in the absence of structural changes, neuronal communication through synchronized activity may dynamically alter the brain's communication and hold great import for understanding and modulating human cognition and behavior (e.g. by sensory selection through entrainment – or phase-locking – of neuronal ensembles; Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008).

Beyond the notion that oscillations are the manifestation of rhythmic fluctuations in neuronal excitability that represent some sort of attentional alignment during stimulus processing, it has been

suggested that oscillations itself encode information that is read by the brain. In this framework, the oscillatory cycle – of which its phase (the fraction of the wave cycle which elapsed since its start) is the key parameter – is thought of as a functional unit that organizes the experience into distinct bits of information (cf. Wilson, Varela, & Remondes, 2015). Accordingly, within an oscillatory cycle, the phase segregates the information to be processed to preserve discriminative power, and during longer computations (which span multiple cycles) related bits of information are linked by their specific phase in order to retain the integrity of the experience. Essentially, the function of such oscillations is to package information into a coherent code for more efficient processing (cf. also Colgin, 2013), and distant brain areas gain access to the encoded information through phase-coherence (i.e. cycle and phase-specific coordinated activity). Hence, the observed reliable occurrence of delta (very slow-wave) oscillations during tasting (across all three studies) can be interpreted as a distinct electrophysiological signature of neural taste processing. Indeed, given that the delta activity was taste-specific (i.e. discriminative of the respective taste quality), it is likely to reflect more than attentional selection.

What benefit may there be for the human brain in recruiting such particularly slow-wave oscillations during tasting? On the one hand, the length of a cycle has been shown to determine the range of the cortical integration and timescale of processing, where slower oscillations reflect a longer trajectory which enables more complex computations (i.e. recruiting more regions within the brain; cf. Engel et al., 2010). This aligns well with our understanding that the gustatory network spans multiple, spatially distributed yet interconnected systems (D. B. Katz et al., 2002), for which delta oscillations pose an ideal candidate to bridge this long spatial trajectory. On the other hand, slow oscillations have been proposed to serve as an internal frame of reference (akin to a metronome) in order to stabilize the encoding of sensory information contained in the spike patterns of single neurons (Panzeri, Ince, Diamond, & Kayser, 2014). This *stabilization* mainly refers to the encoding of natural stimuli where sensory representations have to be created in environments with potentially high degrees of uncertainty with respect to their timing and location[1]. Consequently, the summation of finely timed spike patterns over long time windows necessitates a mechanism that guarantees the integrity of information and perceptual robustness.

In conclusion, I propose that delta oscillations contribute the key mechanism by which information is packaged, transmitted, and read throughout the gustatory network, thereby reflecting the *rhythm of taste* in the human brain. Having established one of the key characteristics of the neural code of tasting should prove helpful for future gustatory research by specifically targeting the delta frequency range. For clinical purposes, taste dysfunction often accompanies aging and several neurodegenerative diseases (cf. Field, 2015), so that the entrainment of the gustatory network with streams of stimulation in the delta-frequency range may support taste functioning (through modification of neuronal response amplitude, latencies, sensory attention, etc.; cf. e.g. Lakatos et al., 2008) – and potentially bring about activity-dependent structural changes. Moreover, brain-computer interfaces – which are at the frontier of neuro interventions in order to restore cognitive functions – may benefit from these findings because they typically rely on band-pass filtering of target frequencies as a quick online processing option (cf. Blankertz, Tomioka, Lemm, Kawanabe, & Müller, 2008). For instance, the BrainCom project strives to continuously decode brain patterns via microelectrode arrays in the inferior frontal cortical region in order to restore speech (cf. Bocquelet, Hueber, Girin, Chabardès, & Yvert, 2016), and the Monash Vision Group develops a neurobionic device to restore vision in blind people with damaged retinas or optical nerves (cf. Rosenfeld & Wong, 2017). Hence, the restoration of taste function using such methodology may be feasible, so long as the central taste system is intact.

[1] Imagine the prolonged stimulation of the gustatory system during the consumption of food. In contrast to an experimental setup with precise unimodal stimulation of the tip of the tongue for 900 ms, here the taste input originates simply from *somewhere* in the oral cavity, for an extended and varying period of mastication, is further confounded by various other variables such as texture and temperature – and all that notwithstanding common cognitive distractions during eating.

6.2 Sequential and parallel processing of taste information

In its most reductionist form a taste-related decision is a binary process that determines an ingested substance as edible or non-edible, to which "spit" and "swallow" constitute the corresponding behavioral responses. To understand how the brain arrives at this simple yet ecologically highly relevant taste-related behavior, one necessarily has to investigate the processing stages that precede the decision (notwithstanding that insights will likely better our understanding of more complex behavior). In order to make an informed choice, the gustatory system requires at the very least some form of object (here taste) recognition, or some feature of the taste that serves as a proxy for edibility.

From research in other sensory systems such as the visual domain we know that humans recognize objects with great speed and ease (Thorpe, Fize, & Marlot, 1996), and that the perceptual categorization of an object (e.g. discriminating a bird from a car) is potentially as rapid as its detection (Grill-Spector & Kanwisher, 2005). Likewise, responses within the olfactory system rapidly encode qualitative odor information (Jiang et al., 2017), though behavioral findings suggest a cascade model of olfactory perception in which brief but distinct processing stages unfold in succession such that odor detection precedes its categorization (Olofsson, 2014). The sequence of processing steps involved in taste recognition has been only explored in behavioral research[2], showing yet again rapid responses to taste stimulation, and – akin to the behavioral olfactory data – with observable delays between simple and more complex evaluations (cf. Halpern, 1986). However, behavioral response times do not only represent sensory processing but also motor- and decision-related components of the response, so that they are ill-suited to resolve the cause of task-related latency differences. To investigate this issue further, I compared both the behavioral and neural responses between two prototypical (binary) taste judgments – a taste-detection (taste vs. water) versus a taste-discrimination task – which are designed to tap into different key components of taste (object) recognition[3].

A considerable limitation to this endeavor is the fact that there are only five established basic taste categories, and they are elicited by chemicals that partly recruit distinct peripheral pathways with different transduction speeds (Roper & Chaudhari, 2017). Hence, not every taste contrast constitutes a sensible option; for instance contrasting salty, which is transduced via fast ion channels, against bitter, which recruits slower G protein-coupled receptors (GPCRs), would potentially reduce the discriminatory task to a "Is this salty or not?" (in fact, such a shift has been termed *time criterion strategy*; cf. Kuznicki & Turner, 1986). As a consequence, the taste-discrimination task in Study 2: The processing sequence involved in taste recognition included only two contrasts: salty against sour (mediated by ion channels), and sweet against bitter (mediated by GPCRs). Matters were complicated then by diverging results amongst these conditions. From the salty-sour discrimination task it appears that there is a clear processing sequence during taste recognition, in which the detection of a taste precedes its categorization considerably. Indeed, such a cascade of distinct processing stages would be in line with prior behavioral findings (e.g. Halpern, 1986; Kuznicki & Turner, 1986) and animal data (Jones et al., 2007). In contrast, the sweet-bitter discrimination revealed quite the opposite: detection and categorization times did not differ from one another. What could be the reason for this difference?

In order to make sense of this contrast specificity, we return to the beginning of this section and must consider the gateway function of the gustatory system. Everything that enters the oral cavity undergoes chemoreceptive scrutiny (Lindemann, 2001), which is to say the system's chief concern is the edibility of a food for which a taste category may serve as a proxy (e.g. bitter suggests potentially toxic compounds; cf. also the introductory section on Taste Perception). However, if indeed categorization subserves a greater cause of determining edibility, then it would surely benefit the system to rapidly encode another

[2]While perhaps not directly applicable to humans, results obtained from research in the rodent gustatory cortex demonstrate taste processing to be a progression of reliable and taste-specific states with clear (though trial-to-trial variable) state transitions of ensemble firing rates (Jones et al., 2007).

[3]In this context it is worth to remind the reader that "sweet" reflects a taste category and not a specific taste such as sucrose. Whereas the ecological value of categorization is evident for both chemosensory systems, object identification appears to be a much more difficult task – perhaps due to its lower relevance (see e.g. Lawless & Engen, 1977)

important taste feature: pleasantness. It should be apparent that the taste qualities are intrinsically coupled with pleasantness[4], and in support of this even newborns show an innate appreciation of sweet (indicated by facial relaxation and sucking), and a rejection of bitter tastes (indicated by mouth gaping; Rosenstein & Oster, 1988). All that is to say: sweet and bitter differ decidedly in their hedonic value, whereas salty and sour converge in this aspect. Consequently, I propose that while the detection of a taste and its categorization may be sequential processing steps in principal (as suggested by the difference between detection and discrimination latencies for salty and sour), the hedonic information is processed in a parallel route to the purely sensory computations and thus has the potential to shrink the gap in timing between the tasks[5], resulting in equal latencies for detection and discrimination of sweet and bitter (for a schematic overview of the proposed processing model, see Figure 6.1).

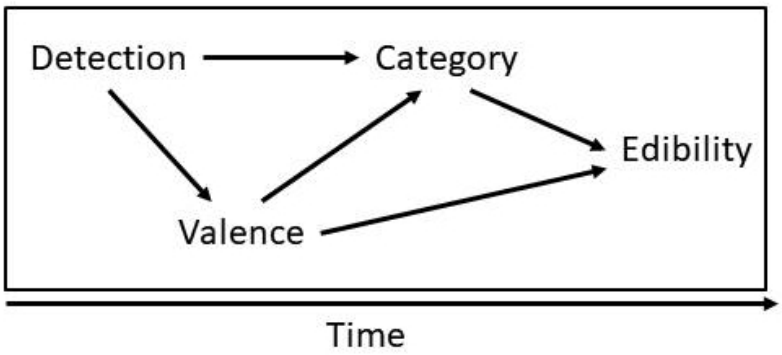

Figure 6.1: A cascade model of gustatory perception. The model proposes four stages in which a taste stimulus is processed: detection of a taste input, the sensory processing that leads to a categorization of the input, the processing of hedonic information in parallel to the sensory evaluations, and finally an edibility judgment. Processing at later stages requires information of earlier steps.

This accords well with findings from animal research which have repeatedly demonstrated that the sequence of taste coding states exerts variability (for a review see Fontanini & Katz, 2008), changes which likely re-arrange the cortical coding to emphasize relevant aspects of a taste episode such as hedonic information. One set of findings is of particular interest, which showed that while the percentage of responding gustatory neurons and their amplitude remained constant, the particulars of the neuronal response changed dramatically (i.e. some lost, acquired, or changed their taste-specificity), specifically increasing the distinctiveness of sweet and bitter tastes according to their emotional valence for rats (whereas the response to identically palatable tastes was unmodified; Fontanini & Katz, 2006). Nevertheless, in humans it was previously deemed unlikely that hedonic representations support the discriminatory function of the sensory computations due to their anatomical segregation in sub-cortical structures and gustatory cortex (Sewards & Sewards, 2002), whereas in rodents such cross-talk is well documented (e.g. Grossman, Fontanini, Wieskopf, & Katz, 2008). Given the present findings and the extensive animal literature, it appears worth to reconsider this notion that sensory and hedonic computations are independent from one another. Surely, the human gustatory system stands to benefit from flexible coding mechanisms that are able to rapidly adapt to highly relevant – even if non-sensory – information, such as the pleasure derived from food.

In conclusion, I interpret these results to demonstrate that taste processing unfolds in a temporal hierarchy with sequential computational states in which detection of a taste precedes its categorization. However, hedonic information appears to be processed in parallel to the sensory input, enabling the gustatory system to incorporate this information where adequate. Consequently, this demonstrates a degree of flexibility in gustatory coding which exceeds prior accounts in humans.

[4]Although it is also important to note that pleasantness may change according to an organism's current state of satiety, attention, etc.; while for instance sweet may generally be pleasant, its hedonic value diminishes with prolonged consumption (e.g. eating one piece of chocolate is enjoyable, the whole bar increasingly less so).

[5]It must be noted that these features are difficult to decouple, and whether the pleasantness then substitutes categorization as the primary proxy (i.e. "Is this pleasant or not?"), or whether it facilities categorization by sharpening the stimulus distinctiveness cannot be discerned from the present findings.

6.3 Shortened taste experience in obese compared to normal-weight individuals

As I have laid out in the Introduction, obesity has become an epidemic to which no end is in sight. This development unfolded in a matter of decades and as such is likely to be in large part due to environmental changes (e.g. the availability of highly palatable and energy-dense foods, inactive lifestyles, etc.), rather than genetic adaptations. Given that not everyone is becoming obese in an environment that presumably favors this affliction, individual differences in the way foods and their associated rewards are neurally encoded gain increasing neuroscientific interest (cf. Small, 2009). For instance, one by now well-supported hypothesis is that obese individuals have a blunted reward response so that food is overconsumed in order to compensate for this deficiency (which relates closely to alcoholism and other addictive disorders; cf. Blum et al., 2000). Additionally, cue reactivity (the sensitivity to food cues) appears to be heightened (Stoeckel et al., 2008), so that homeostatic signals such as satiety are more likely to be ignored. These two observations demonstrate both hypo- and hyperactive neural responses, and are unified by the proposition that individuals with high sensitivity to reward are at risk for overconsumption, which in turn causes neural adaptations in the dopamine system resulting in reduced pleasure (Davis, Strachan, & Berkson, 2004). These examples are but few of the many factors contributing to this complex issue, and research into the perception of flavor, and more specifically the perception of taste, are invaluable components of the ongoing research on obesity.

To this end, in Study 3: Contrasting taste processing between normal-weight and obese individuals I was granted an ideal opportunity to contribute to aforementioned research by investigating whether individuals from these populations exert observable differences in their neural patterns of sensory taste information coding, and their respective temporal dynamics. Based on the indistinguishable activation patterns during stimulation, my findings indicate that individuals from these groups do not appear to differ in their immediate sensory taste response. Furthermore, the results obtained from the temporal generalization method suggest that in either case two distinct mental processes underly the representations, of which the first is a brief state that is likely related to a detection response, and the second process is an ongoing state which likely reflects a more in-depth stage of taste encoding concerned with categorization. Interestingly, in obese individuals the response diminished almost immediately with the offset of stimulation, at which point the groups start to differ. This feeds well into the narrative of hypoactive neural responses in obesity, such that the taste experience itself subsides earlier for these individuals (similarly to an attenuated reward response). Given the brevity of this effect it seems prudent to first strive for replication of this finding, and to test whether it is of any practical consequence to behavior, before drawing far-reaching conclusions.

In summary, normal-weight and obese individuals largely converge in the way they encode sensory taste information, although the duration of gustatory processing appears to differ between them. This result could point to a shorter-lived taste experience as another part of the vicious cycle of obesity in which attenuated responses in combination with heightened cue reactivity cause overconsumption.

6.4 Conclusion

I have dedicated my PhD research to furthering our understanding of how the human gustatory system functions. To this end, I have contributed to the research field by finding that delta oscillations are likely one of the key mechanisms by which the brain encodes taste information. Furthermore, my research suggests that the human gustatory system is adaptable in its processing of information, both to contextual factors that determine the allocation of attention, and to hedonic evaluations – a flexibility which was previously only demonstrated in animal models. Finally, I joined the ongoing endeavor to unravel the multi-faceted affliction of obesity by supplementing current knowledge with the possibility of hypoactive sensory taste encoding responses in obese individuals.

It comes as no surprise that I conclude my dissertation with the call for further research – if ever there was an understudied area of inquiry – and unjustifiably so – surely the human gustatory system should qualify. The reason for this deficit presumably lies with the difficulties of studying the sense of taste in a controlled environment. Nevertheless, much is to gain from such investigations, and with advances in technology and methodology future efforts are likely to bear fruit.

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